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Timing of the Most Recent Device Procedure Influences the Clinical Outcome of Lead-Associated Endocarditis

Results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort)

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Objectives The purpose of this study was to determine whether the timing of the most recent cardiac implantable electronic device (CIED) procedure, either a permanent pacemaker or implantable cardioverter-defibrillator, influences the clinical presentation and outcome of lead-associated endocarditis (LAE).

Background The CIED infection rate has increased at a time of increased device use. LAE is associated with significant morbidity and mortality.

Methods The clinical presentation and course of LAE were evaluated by the MEDIC (Multicenter Electrophysiologic Device Cohort) registry, an international registry enrolling patients with CIED infection. Consecutive LAE patients enrolled in the Multicenter Electrophysiologic Device Cohort registry between January 2009 and May 2011 were analyzed. The clinical features and outcomes of 2 groups were compared based on the time from the most recent CIED procedure (early, <6 months; late, >6 months).

Results The Multicenter Electrophysiologic Device Cohort registry entered 145 patients with LAE (early = 43, late = 102). Early LAE patients presented with signs and symptoms of local pocket infection, whereas a remote source of bacteremia was present in 38% of patients with late LAE but only 8% of early LAE ($p < 0.01$). Staphylococcal species were the most frequent pathogens in both early and late LAE. Treatment consisted of removal of all hardware and intravenous administration of antibiotics. In-hospital mortality was low (early = 7%, late = 6%).

Conclusions The clinical presentation of LAE is influenced by the time from the most recent CIED procedure. Although clinical manifestations of pocket infection are present in the majority of patients with early LAE, late LAE should be considered in any CIED patient who presents with fever, bloodstream infection, or signs of sepsis, even if the device pocket appears uninfected. Prompt recognition and management may improve outcomes. (J Am Coll Cardiol 2012;59:681–7) © 2012 by the American College of Cardiology Foundation

Implantation of cardiac implantable electronic devices (CIEDs), both permanent pacemakers and implantable cardioverter-defibrillators (ICDs), has dramatically increased (1,2). This increase has been driven by the needs of an aging population coupled with the expanded indications for ICDs (3–5). However, the CIED infection rate has also been increasing (6–8). Device infection is associated with significant financial costs, morbidity, and mortality, requiring aggressive treatment (9,10). Infection can present as either local involvement at the device pocket or a systemic

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Abbreviations and Acronyms

CIED = cardiac implantable electronic device

CoNS = coagulase-negative staphylococci

ICD = implantable cardioverter-defibrillator

LAE = lead-associated endocarditis

syndrome that is associated with bloodstream infection, with or without lead and valve endocarditis. The clinical presentation of lead-associated endocarditis (LAE) is variable (9,11–14). In the present analysis, we sought to determine whether the timing of the most recent CIED procedure influences the clinical presentation and outcome of LAE.

Methods

The MEDIC (Multicenter Electrophysiologic Device Infection Cohort) registry is an international registry consisting of 10 academic medical centers (see Online Appendix for a list of enrolling centers) that prospectively enroll patients with CIED infections. We analyzed patients with a diagnosis of LAE who were enrolled in the MEDIC registry between January 2009 and May 2011. The present study was conducted to determine whether the time from the most recent CIED procedure influences the risk factors, clinical presentation, and microbiology of LAE. The local institutional review board at each site approved the study protocol. Patients were followed for 6 months after enrollment in the MEDIC registry. Patient demographic, clinical, and laboratory data at the time of LAE diagnosis and treatment outcomes were entered into the MEDIC registry database.

Definitions. The diagnosis of LAE was based on the modified Duke criteria (10,15). LAE was present if there was persistent bloodstream infection, documented by positive blood cultures and the presence of lead vegetation documented by echocardiography. Patients with unexplained fever and persistent unexplained bloodstream infection in the absence of a documented intracardiac vegetation were also included in the analysis if their symptoms resolved after removal of a CIED. Another group of patients with LAE were those patients with an unexplained intracardiac vegetation who presented with local pocket or systemic symptoms but had already been treated with antibiotics.

A vegetation was defined as an oscillating intracardiac mass on a pacemaker or ICD lead or cardiac valve that was present in >1 echocardiographic plane. Early LAE was defined as signs and symptoms that occurred within 6 months of the most recent CIED procedure. If LAE signs and symptoms occurred >6 months after surgery, it was defined as late LAE.

The time from the most recent CIED procedure was measured in months. A revision procedure included a pulse generator replacement, lead revision, and system upgrade. The initial implantation was defined as the first CIED procedure. All subsequent procedures were, therefore, classified as revisions.

To assess medical comorbid conditions, we used the Charlson Comorbidity Index, which consists of 19 different disease comorbidity categories, weighted from 1 to 6 based on adjusted relative risk of 1-year mortality and summed to provide a total score (16). The Charlson Comorbidity Index was previously validated as a predictor of mortality in patients with a permanent pacemaker (17).

Diagnosis and treatment. Multiple blood cultures were obtained in each patient. The diagnosis of an intracardiac vegetation was made by either transthoracic or transesophageal echocardiography. All patients underwent either percutaneous or open surgical removal of all hardware. Lead and pulse generator pocket cultures were obtained. After the procedure, the patients received a prolonged course of intravenous antibiotics based on published guidelines (10). Reimplantation was performed at the discretion of the primary physician. Patients were followed for 6 months from the date of enrollment. A relapse was defined as a recurrence of infection with the same organism based on antimicrobial sensitivity.

Statistical analysis. Summary statistics (mean ± SD, median, interquartile range, and frequency distribution) were generated for patient demographic information and baseline clinical presentation to characterize the study population. A chi-square test or Fisher exact test was used to compare categorical variables between early and late LAE patients. Continuous variables were compared using a 2-sample *t* test or Wilcoxon sum rank test, as appropriate. All tests were 2-sided, and a p value <0.05 was considered statistically significant.

Results

Patient demographics. A total of 145 patients with LAE were prospectively identified and enrolled in the MEDIC registry. Forty-three cases of LAE occurred within 6 months of a CIED procedure and were classified as early LAE, whereas the remaining 102 cases occurred >6 months after a CIED procedure and were classified as late LAE. The patient demographics of the 2 groups are summarized

Table 1 Patient Demographics

	Early (n = 43)	Late (n = 102)	p Value
Age, yrs	66 ± 15	63 ± 16	NS
Male	74.4	67.6	NS
PM/ICD	15 (35)/28 (65)	50 (4)/52 (51)	NS
Most recent procedure			0.03
Initial implantation	15 (35)	56 (55)	
Revision	28 (65)	46 (45)	
Months from most recent procedure	1.9 (1, 3.5)	26.2 (17, 41.2)	
No. of leads	2.4 ± 0.8	2.4 ± 0.87	NS
Ejection fraction, %	34.5 ± 17.6	32.7 ± 15.2	NS
Vegetation size, mm	8.5 (4.2, 17.2)	10 (5, 20)	NS

Values are mean ± SD, %, n (%), or median (25th, 75th percentile).
ICD = implantable cardioverter-defibrillator; PM = permanent pacemaker.

in Table 1. The groups were similar with respect to age, sex, and type of CIED, although early LAE patients had a higher percentage of ICDs (65% vs. 51%, p = NS). The most recent CIED procedure in early LAE patients was a system revision in 28 of 43 (65%) compared with 46 of 102 of late LAE patients (45%) (p = 0.03). More than half of late LAE patients (55%) had a single procedure, which was their initial CIED implantation. The total number of CIED procedures was similar for both groups (2 ± 1 vs. 1.7 ± 0.91, p = NS). There was a history of CIED infection in 16% of early LAE patients and 9% of late LAE patients.

The groups were similar with respect to major comorbid conditions (Table 2) except that a higher percentage of late LAE patients were on hemodialysis (early = 5% vs. late = 19%, p = 0.037). Multiple medical comorbid conditions were present in a majority of the study population. The Charlson Comorbidity index score was similar in the 2 groups (3 ± 2.25 vs. 3 ± 2.46, p = NS). The most common comorbidity was heart failure. The mean left ventricular ejection fraction was 34.5 ± 17.6% in the early LAE group and 32.7 ± 15.2% in the late LAE group (p = NS).

The presenting symptoms of LAE differed based on the time from the most recent CIED procedure (Table 3). Patients with early LAE more frequently presented with signs of local pocket infection that included erythema, pain, swelling, warmth, and pus or drainage from the pocket. In contrast, the majority of patients with late LAE had signs of systemic infection, such as fever, chills or sweats, and signs of sepsis. Peripheral emboli and signs of metastatic infection were seen infrequently and were not different between the 2 groups. There was echocardiographic evidence of lead vegetation in 63% of early LAE patients compared with 82% of late LAE patients (p < 0.01). The patients without vegetation were diagnosed with LAE because they had persistent bloodstream infection without an identifiable cause and their symptoms resolved once their CIED hardware was removed. In early LAE patients, the lead vegetation was detected by transthoracic echocardiography in 11 of 43 (26%), whereas transesophageal echocardiography was required in 16 of 43 (37%). No vegetation was seen by either modality in 37%. In contrast, in late LAE patients, transthoracic echocardiography detected the vegetation in only 23 of 102 (23%), whereas transesophageal echocardiography was required in 60 of 102 patients (59%) to detect the lead vegetation. The remaining 18% had no vegetation detected. The median vegetation size was similar in both groups (early = 8.5 mm vs. late = 10 mm). In addition, a vegetation was present on an intracardiac valve in 18 of 43 (42%) early LAE patients and 31 of 102 late LAE patients (29%). In early LAE patients, there was evidence of a vegetation on the aortic valve in 4 (21%), the mitral valve in 6 (32%), the tricuspid valve in 6 (32%), and the pulmonic valve in 2 (15%). In contrast, late LAE patients had evidence of a vegetation on the aortic valve in 5 (16%), the mitral valve in 6 (19%), the tricuspid valve in 18 (58%), and the pulmonic valve in 2 (7%).

Table 2 Patient Comorbidities

	Early (n = 43)	Late (n = 102)	p Value
CABG surgery	11 (26)	28 (28)	NS
Heart failure	15 (33.3)	22 (22)	NS
Hemodialysis	2 (5)	19 (19)	0.037
Prosthetic valve	6 (14)	12 (12)	NS
Anticoagulation	13 (30)	21 (21)	NS
Immunosuppressive use	3 (7)	4 (4)	NS
Steroid use	3 (7)	4 (4)	NS
Implanted central catheter	4 (9)	20 (20)	NS
Vascular graft	4 (9)	12 (12)	NS
Charlson Comorbidity Index	3 ± 2.25	3 ± 2.46	NS

Values are n (%) or mean ± SD.
CABG = coronary artery bypass graft.

Table 3 Presenting Symptoms

	Early (n = 43)	Late (n = 102)	p Value
Signs of local infection			
Erythema	19 (44)	11 (11)	<0.001
Pain	16 (37)	14 (14)	0.004
Swelling	16 (37)	9 (9)	<0.001
Warmth	17 (40)	7 (7)	<0.001
Pus	9 (21)	4 (4)	0.003
Drainage	12 (28)	6 (6)	0.001
Signs of systemic infection			
Fever >38°C	26 (61)	82 (80)	0.02
Chills/sweats	25 (58)	80 (78)	0.03
Sepsis	13 (30)	48 (47)	<0.05
Peripheral signs			
Emboli	3 (7)	14 (14)	NS

Values are n (%).

The source of the bloodstream infection differed between the groups (Fig. 1). The CIED wound or CIED device site was commonly identified as the source of infection in early LAE (54%); this was not the case in late LAE (11%, p = 0.001). A remote source of infection, such as a vascular catheter (4%) and the gastrointestinal tract (1%), was identified in a minority (8%) of early LAE patients. In contrast, late LAE patients more commonly had a remote source of infection identified (38%, p < 0.01). Remote sources of infection included vascular catheters (15%), infected atrioventricular fistulae (4%), localized abscess (3%), and osteomyelitis (6%).

Bacteriology. Blood cultures were positive in 31 of 43 early LAE patients (72%) and 95 of 102 late LAE patients (93%). CIED pocket cultures were positive in 25 of 39 early LAE patients (62%) compared with 30 of 89 of late LAE patients (34%) (p = 0.011). No pocket culture was obtained in 4 early LAE patients and 13 late LAE patients. Lead cultures were positive in 24 of 39 early LAE patients (62%) and 40 of 88 late LAE patients (46%) (p = NS). No lead culture was obtained in 4 early LAE patients and 14 late LAE patients. Staphylococci were the most frequent pathogens in

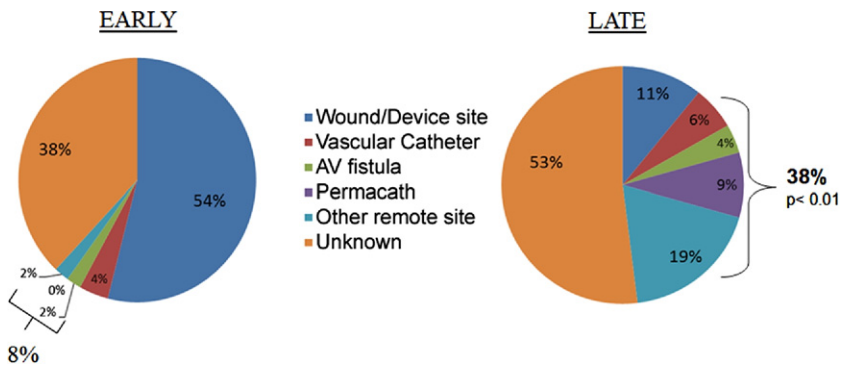

Figure 1 Source of Bloodstream Infection

The time from the most recent cardiac implantable electronic device procedure influenced the source of bacteremia. The source of bacteremia was a wound or device site in 54% of early lead-associated endocarditis (LAE), but only 11% of late LAE ($p = 0.001$). A remote source of bacteremia was present in 38% of late LAE patients but only 8% of early LAE patients ($p < 0.01$). AV = atrioventricular.

LAE (Fig. 2). Staphylococcal species were cultured in 51% of early LAE patients and 67% of late LAE patients (p = NS). *Staphylococcus aureus* was the most common cause of LAE (15 of 43 early LAE vs. 42 of 102 late LAE), followed by the coagulase-negative staphylococci (CoNS) (7 of 43 early LAE vs. 25 of 102 late LAE) and streptococci. Methicillin resistance was present in 5 of 15 early LAE patients (30%) and 18 of 42 late LAE patients (23%) infected with *S. aureus*. No organism could be cultured in 28% of the early LAE patients and 5% of the late LAE patients.

Outcome. The CIED device and leads were removed at the time of presentation in all cases. A laser sheath was required for lead removal in 56% of early LAE patients and 64% of late LAE patients. The entire system was successfully removed in all but 2 of 43 (5%) early LAE patients and 4 of 102 late LAE patients (4%) (p = NS). Some residual lead material remained in the 2 early LAE patients and 4 late LAE patients. No patient required conversion to open thoracotomy. Pulmonary emboli after CIED removal occurred in 1 early LAE patient (2.3%) and 6 late LAE patients (6%). In-hospital mortality was 7% in the early LAE group and 6% in the late LAE group. Patients were treated with intravenous antibiotics for a median of 42 days (25th, 75th percentiles: early LAE = 34, 52 days, late LAE = 30, 52 days). A new CIED device was implanted in 44% of the early LAE group and 53% of the late LAE group. Complete 6-month follow-up data were available for 24 of 43 early LAE patients (56%) and 63 of 102 late LAE patients (62%). One patient in each group had recurrent LAE. Six-month mortality was 25% in early LAE patients and 29% in late LAE patients.

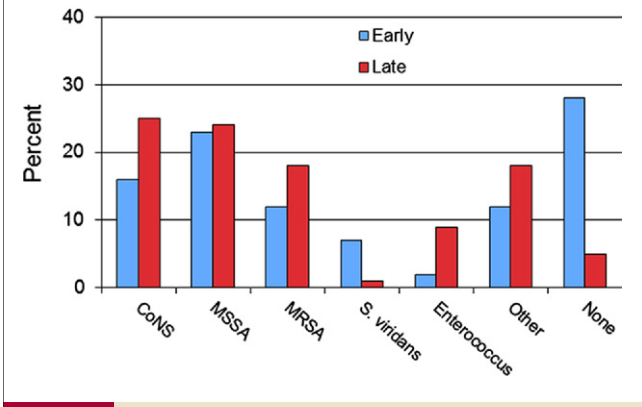

Figure 2 Microbiology of Lead-Associated Endocarditis

CoNS = coagulase-negative staphylococci; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

Discussion

Our evaluation of a large, prospective, multicenter cohort of patients with LAE provides significant insights that include the following: 1) the clinical presentation of LAE is influenced by the time from the most recent CIED procedure; 2) patients in whom LAE develops within 6 months of a CIED procedure usually present with signs and symptoms associated with local CIED pocket site infection; 3) LAE may develop months or years after a CIED procedure; 4) patients who present with signs and symptoms of systemic infection often have identifiable remote sites of infection; 5) in-hospital mortality is 6% to 7%; and 6) the recurrence rate is low in surviving patients.

Increasing CIED infection burden. The CIED implantation rate has dramatically increased over the past 2 decades, driven by the increase in ICD use (1,2,6). Recent data suggest that although overall complications associated with CIED implantation have decreased, the infection burden has increased (7,8,18–20). Infection after CIED implantation remains a major complication with significant

morbidity and mortality, coupled with tremendous financial costs (21).

Clinical presentation of LAE: early versus late. CIED infection may present as either local CIED pocket infection or systemic bloodstream infection associated with LAE. Prompt recognition and treatment of CIED infection are imperative because morbidity and mortality remain high with untreated infection. Effective treatment of CIED infection, either local or systemic infection, requires removal of all hardware.

LAE represents 19% to 23% of total CIED infections (22,23). Although LAE may occur soon after a CIED procedure, patients with LAE can present months or years later. It is not known why systemic infection and LAE develop in a limited number of patients with local CIED infection. Previous studies have emphasized the importance of patient comorbid conditions including multiple device revisions in LAE predisposition (9–13,24,25). Another contributing factor may be a delay in the optimal management of local pocket infection. Many of our patients with early LAE received antibiotics for some time before their transfer to a MEDIC center for removal of all CIED hardware. The duration of previous antibiotic therapy is not known. A recent study showed that a delay in CIED removal is associated with increased morbidity and mortality (26).

The present analysis demonstrates that the time from the most recent CIED procedure influences the clinical presentation of LAE. Patients in whom LAE develops soon after a CIED procedure often present with signs of local inflammation with bacteremia due to the organism responsible for the local infection. In our study, the median time from the most recent procedure was 1.9 months. Klug et al. (11) found that 14 of 52 patients (27%) with pacemaker LAE presented within 6 weeks of their last pacemaker-related procedure. Signs of local pocket inflammation were evident a mean of 4 days post-procedure. Differences in patient demographics may explain a disparity in the timing and clinical presentation of early LAE.

By contrast, the majority of our patients with late LAE presented with signs of systemic infection such as fever, chills, sweats, and signs of sepsis. Infection presented a median of 26.2 months after the most recent procedure. Remote sources of infection were common. In our patients with late LAE, 6% had vascular catheters such as peripheral or central intravenous catheters, 9% had permanent hemodialysis catheters, and 4% had atrioventricular fistulae as the likely remote source of bacteremia. In addition, 19% of patients had an identifiable noncatheter-related source of bacteremia such as an abscess and osteomyelitis remote from the pulse generator site. Patients with late LAE had multiple medical comorbid conditions including the high prevalence of long-term hemodialysis in 19% of the cases. The frequent need for vascular access is likely a contributing factor.

Bacteriology and diagnosis of LAE. In our series, *S. aureus* was the most common pathogen isolated in both early and late LAE, consistent with previous publications that reported that staphylococcal species were the predominant organisms responsible for LAE in more than two thirds of cases (9,11,13). Earlier investigators have also demonstrated that CIED recipients with *S. aureus* bacteremia are particularly at high risk of LAE (27–29). This association is likely due to hematogenous seeding of the CIED device after *S. aureus* bacteremia. It further underscores the importance of managing vascular access catheters in CIED patients because these may represent portals for bacteremia. Earlier investigations have also highlighted the role of drug-resistant pathogens in LAE (30). In our series, methicillin-resistant *S. aureus* was responsible for 16% of LAE (early = 12%, late = 18%). However, LAE was also caused by organisms other than *S. aureus*. Skin flora, such as CoNS, are common pathogens isolated in LAE. In 1 series, CIED infection was present in 36% of patients with CoNS bacteremia and 20% of non–*S. aureus* gram-positive cocci (31). Therefore, LAE should be considered in any CIED patient in whom gram-positive bacteremia develops, regardless of the organism.

In general, a diagnosis of LAE relies on the finding of an intracardiac vegetation on echocardiography and documentation of persistent bloodstream infection (10). Transesophageal echocardiography is often required to make the diagnosis (9,14,32). However, LAE should also be considered in CIED patients who have persistent bacteremia without an identifiable source, even if the echocardiogram is inconclusive. In our study, 38% of early and 18% of late LAE patients had no vegetation detectable by either transthoracic or transesophageal echocardiography. However, clinical manifestations of infection resolved in all these patients on complete removal of CIED hardware and with systemic antibiotic therapy, suggesting underlying device infection. Consequently, the importance of obtaining blood cultures in any patient with a CIED who presents with signs and symptoms of pocket infection or a systemic illness cannot be overemphasized. Transesophageal echocardiography should be pursued if the findings on transthoracic imaging are negative or inconclusive. This is especially important in CIED recipients who present with unexplained fever or bacteremia without a clear source.

Treatment of LAE. Treatment of LAE requires removal of all CIED hardware and a prolonged course of intravenous antibiotics (9–11,13,14). Lead removal can be accomplished in >95% of cases without the need for open heart surgery (10,33). The LEXICON (Lead Extraction in the Contemporary Setting) study evaluated the safety and efficacy of laser-assisted lead extraction in a diverse group of 1,149 consecutive patients. The indication for lead extraction was CIED infection in 56.9%, including 29.2% who had LAE. Clinical success was achieved in 98.8%, with a major adverse event rate of 4.0%. However, mortality in the LAE group was 4.3% despite CIED removal. In our series

of 145 patients with LAE, there was only 1 procedural death and few other serious sequelae such as pulmonary emboli, despite removing leads percutaneously with vegetations that averaged >10 mm in diameter. Prolonged treatment of LAE with systemic antibiotics is recommended (10), although a shorter duration of treatment is possible if endocarditis is confined to the right heart (9). With modern aggressive therapy, reported in-hospital mortality from LAE ranges from 4% to 7% (9–11,13,14). Mortality, in part, depends on the causative agent, as LAE caused by *S. aureus* is associated with a poorer outcome compared with CoNS.

Many patients undergoing CIED extraction for infection require ongoing device therapy, and reimplantation of a new CIED is warranted. The optimal timing of device reimplantation in patients with LAE has not been determined. In general, most experts believe that a CIED device may be reimplanted in infected patients once the CIED has been removed and blood cultures are consistently negative (9). However, a longer waiting time may be reasonable in patients with valvular endocarditis.

Study limitations. The decision to use the 6-month time point to define early versus late LAE was arbitrary. It is possible that other time points could be used for analysis. Nonetheless, the use of the 6-month definition did provide useful information to distinguish the clinical presentations of early versus late LAE. Our analysis included patients who had persistent bloodstream infection without evidence of an intracardiac vegetation because their symptoms resolved after removal of their CIED. Previous investigation showed that the 1-year mortality of patients with bloodstream infection is similar to those with documented vegetations (26). We recognize that the patient population studied reflects those referred to academic medical centers for treatment and may not be representative of all patients with LAE. In addition, 6-month follow-up data were not available for all patients because many patients were referred to the study centers for initial treatment of LAE but returned to their local medical centers for continued care. Our data may, therefore, underestimate both the true LAE relapse rate and 6-month mortality rate.

Conclusions

LAE is a serious complication of CIED implantation that is associated with considerable morbidity and mortality. Complete CIED removal is necessary for attempted cure, which also involves prolonged antimicrobial therapy. The clinical presentation of LAE is influenced by the time from the most recent CIED procedure. Although clinical manifestations of pocket infection are present in the majority of patients with early LAE, late-onset LAE should be considered in all CIED patients who present with fever, bloodstream infection, or signs of sepsis even if the device pocket is ostensibly uninfected. Prompt recognition and management may improve clinical outcomes.

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Key Words: endocarditis ■ implantable cardioverter-defibrillator ■ permanent pacemaker.

APPENDIX

For a list of enrolling centers, please see the online version of this article.